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Heart Failure and Cardiomyopathies

DIFFERING PATTERNS OF MYOSTATIN SIGNALING REGULATE HYPERTROPHY IN SEVERE AORTIC STENOSIS AND HYPERTROPHIC CARDIOMYOPATHY

Poster Contributions
Hall C
Monday, March 31, 2014, 9:45 a.m.-10:30 a.m.

Session Title: Heart Failure and Cardiomyopathies: Prognostic Factors and Determinants of Outcomes in Heart Failure Patients
Abstract Category: 12. Heart Failure and Cardiomyopathies: Clinical
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Authors: *Estibaliz Castillero, Hirokazu kashi, Halit Yerebakan, Robert Sorabella, Marc Najjar, Klara Pendrak, Catherine Wang, Ziad Ali, Donna Mancini, Jeannine D'rmiento, H. Lee Sweeney, P. Christian Schulze, Isaac George, Columbia University, New York, NY, USA, University of Pennsylvania, Philadelphia, PA, USA*

Myostatin (MSTN), a negative regulator of muscle growth, is induced by cardiac overload and may regulate the transition from physiologic hypertrophy to ventricular dilatation. We hypothesized that patients with severe aortic stenosis (AS) and hypertrophic cardiomyopathy (HCM) have distinctive anti-hypertrophic signaling.

Serum was collected from AS patients before aortic valve replacement (n=16). Serum and cardiac tissue samples were collected during septal myectomy/heart transplant in patients with HCM (n=10). Western blot was performed for MSTN, IGF-I, Akt, P-Akt, p38, P-p38, SMAD2/3 and P-SMAD2/3. MiR1, miR133a (prohypertrophic) and miR208a (anti-hypertrophic) were measured by qPCR. Non-failing heart samples (n=4) and donor serum (n=10) served as control.

AS patients showed increased MSTN/IGF-1 and miR-208a, and decreased miR-1 and miR-133a, suggesting the activation of an anti-hypertrophic program. On the contrary, in HCM, increased IGF-I and cardiac P-Akt together with decreased MSTN/SMAD2/3 and unchanged P-p38 suggested an ongoing pro-hypertrophic program.

These results suggest different MSTN regulation in AS and HCM hypertrophy. In AS, increased MSTN may act to prevent pathological hypertrophy. In contrast, IGF-I/Akt physiologic and pro-hypertrophic signaling together with lack of p38/MSTN anti-hypertrophic mechanism may mediate non-pathological hypertrophy in HCM. MSTN activation may be a compensatory mechanism to prevent hypertrophy in pathological cardiac states.

Table 1. Cardiac remodeling markers (*p<0.05 vs. Normal)

	Normal (n=4-10)	HCM (n=10)	AS (n=16)	p
Cardiac MSTN Serum MSTN	100 ± 5.8 100 ± 0.1	69.4 ± 3.1* 84.8 ± 0.8*	n/a 157± 11.45*	<0.001 <0.001, <0.001
Cardiac IGF-I Serum IGF-I	100 ± 0.24 100 ± 2.4	105.1 ± 4.7 167.7 ± 12.3*	n/a 109.1 ± 7.9	0.585 0.0301, 0.460
Cardiac P-SMAD2/3/SMAD2/3	100 ± 2.2	79.3 ± 1.8*	n/a	0.002
Cardiac P-Akt/Akt	100 ± 2.5	130.1 ± 5.6*	n/a	0.025
Cardiac P-p38/p38	100 ± 0.2	88.8 ± 4.6	n/a	0.252
Cardiac miR-1 Serum miR-1	1 ± 0.2 1 ± 0.2	0.76 ± 0.2 n/a	n/a 0.28 ± 0.07*	0.528 0.004
Cardiac miR-133a Serum miR-133a	1 ± 0.1 1 ± 0.1	0.72 ± 0.1 n/a	n/a 0.62 ± 0.09*	0.237 0.036
Cardiac miR-208a Serum miR-208a	1 ± 0.2 1 ± 0.1	3.39 ± 0.6* n/a	n/a 2.08 ± 0.48*	0.023 0.033